PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
61.78608/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/02928	07.07.2003	10.07.2002
International Patent Classification (IPC) or both national classification and IPC		
C07K1/22		
Applicant		
NATIONAL BLOOD AUTHORITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.01.2004	16.07.2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02928

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34	as originally filed

Claims, Numbers

1-6, 15-20	as originally filed
7-14	filed with telefax on 11.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 11-20

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11-20 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-10
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	2-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

   see separate sheet

Section III

1) The subject-matter of claims 11 and 12 is defined by the process of producing fibrinogen rather than by the technical features of the particular fibrinogen preparation. As such, the scope of said subject-matter is unclear to such an extent that a meaningful examination is not possible. Claims 13 - 20 relate back / are dependent on said claims.

2) Some of the features in the kit claim 14 relate to a method of producing the kit rather than clearly defining the kit in terms of its technical features. The intended limitations are therefore not clear from this claim, contrary to the requirements of Article 6 PCT.

Section V

1) Reference is made to the following documents:

D1: JP(A) 02193913
D2: Millipore Product Catalogue - Product Category Prosep Chromatography Media (1999), , 1-2
D3: Haemophilia: The Official Journal Of The World Federation Of Hemophilia. England Nov 2000 (11-2000), 6(6), 705-708
D4: Derwent WPI; AN: 1996-112641(JP(A) 8012586)
D5: WO-A-9012803 & US-A-5 169 936 (cited on page 3 of the description)
D6: Journal Of Biomedical Materials Research (05-2000), 50(2), 110-113
D7: Derwent WPI; AN: 1997-095485(JP(A) 8333387)

2) The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claim 1 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

D5 (page 21) proposes to purify fibrinogen with an immobilized metal affinity chromatography resin; the said disclosure would appear not to go beyond mere speculations.

On the other hand, it is known from D1 and D2 (section headed "Prosep Chelating I, II and III) that fibrinogen binds to metal chelating chromatography media. In its

introductory portion, D2 (see section headed "Description") discloses that the thereafter described media are efficient as the first capture step in the purification process of a protein from cell culture. Cell culture is to be regarded as containing several proteins binding to at least some extent to metal ion affinity chromatography matrix.

Thus, it is considered that D2 constitutes an enabling disclosure prejudicial to the subject-matter of claim 1.

3) The subject-matter of independent claims 3, 7, 8, 9 and 10, and claims 4 - 6 as dependent thereon would appear to be novel and inventive in view of the known prior art (Art. 33(2), (3) PCT; see, however, item 6, below).

None of the known prior art documents discloses or renders obvious that fibrinogen could be separated from plasminogen by means of metal ion affinity chromatography (IMAC), that fibrinogen and plasminogen could be prepared by IMAC, or that fibrinogen and factor XIII could be co-purified using the said medium.

It would appear to be generally acknowledged that the binding properties of proteins to affinity media cannot a priori be reasonably predicted.

It should be noted that fibrinogen e.g. does not bind to Cu immobilized cellulose affinity membrane and hydroxyapatite treated with a metal salt (see D6, D7)

4) For analogous reasons, the subject-matter of claim 2 would appear to be novel and inventive (Art. 33(2), (3) PCT).

5) Note in relation to claims 11 - 20:

It would appear that the use of fibrinogen in therapy is known in the prior art (see e.g. D3, D4). A new process of producing a known product (eg plasminogen free fibrinogen) cannot render the said product novel. As regards claims 14 and 16: replacement therapy in afibrinogenaemia as well as virus inactivation of pharmaceutical compositions derived from human blood is known to the skilled person (see documents cited in the present application).

6) The use of the term "preparation" where most likely "separation and purification" is

intended renders the scope of claim 9 unclear (Art. 6 PCT).

Under the above assumption, it would appear that also claim 9 should be dependent on claim 8.

7) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor are these documents identified therein.

7. A method for the co-purification of fibrinogen and factor XIII which comprises the steps of:

(a) loading a solution comprising fibrinogen and factor XIII onto an immobilised metal ion affinity chromatography matrix under conditions such that the fibrinogen and the factor XIII both bind to the matrix, and

(b) selectively co-eluting the fibrinogen and the factor XIII from the matrix.

8. Use of immobilised metal ion affinity chromatography for the separation of fibrinogen from plasminogen.

9. Use of immobilised metal ion affinity chromatography for the preparation of fibrinogen and plasminogen.

10. Use of immobilised metal ion affinity chromatography for the co-purification of fibrinogen and factor XIII.

11. Fibrinogen prepared by a method according to any of claims 1 to 7.

12. Fibrinogen prepared by a method according to any of claims 1 to 7, for use in therapy.

13. A pharmaceutical kit comprising fibrinogen prepared by a method according to any of claims 1 to 7, together with thrombin.

14. A kit as claimed in claim 13, wherein the thrombin is prepared by a method comprising the steps of:

(a) solvent-detergent virus inactivation of a solution comprising prothrombin and factor X;

(b) loading the product of step (a) onto an anion